KnowYourNumber™

The Key To Proactive Good Health

BioSignia™

HEALTHCARE TECHNOLOGY FOR LIFE

Predictions in Health Care

- **Claims-based Predictions**
  - Based on diagnostic codes and historical utilization of services
  - Predict future costs and target high-utilizers for disease management
  - Uses medical *claims* data
- **Credit/debit assessments**
  - Based on *mortality* – likelihood of *death* in a group of people with certain characteristics
  - Prediction of health status, “health quotients”, “health age”, life expectancy etc.
  - Self-reported
  - May include lab tests and support limited morbidity assessment
- **Individualized Disease-specific Risk Assessment**
  - Based on *morbidity* – likelihood of *disease onset* within a specified time using multivariate regression
  - Prediction of actual disease or complications onset
  - Uses targeted evidence-based clinical assessment
  - Employs lab information targeted to specific disease or complication
- **Diagnosis**
  - Based on morbidity evaluation algorithm
  - Establishes actual disease or complication from a set or single (surrogate) marker
  - Employs lab information targeted to specific focus

Synthesis Modeling™

- A unique method to develop empirical prediction equations for chronic diseases.
  - Employs multivariate meta-analysis
  - Allows continuous updating with new clinical discovery ("Evergreen")
    - Improvement to existing models
  - Comprehensive
    - Create de novo models
    - Allows expanded morbidity predictions
  - Accurate
    - Excellent correlation to longitudinally-derived models.
  - Facilitates creation of applied solutions
    - Chronic care management
    - Disease and population health management
    - Quality of care and treatment efficacy
    - Pay-for-performance
    - Mortality assessment

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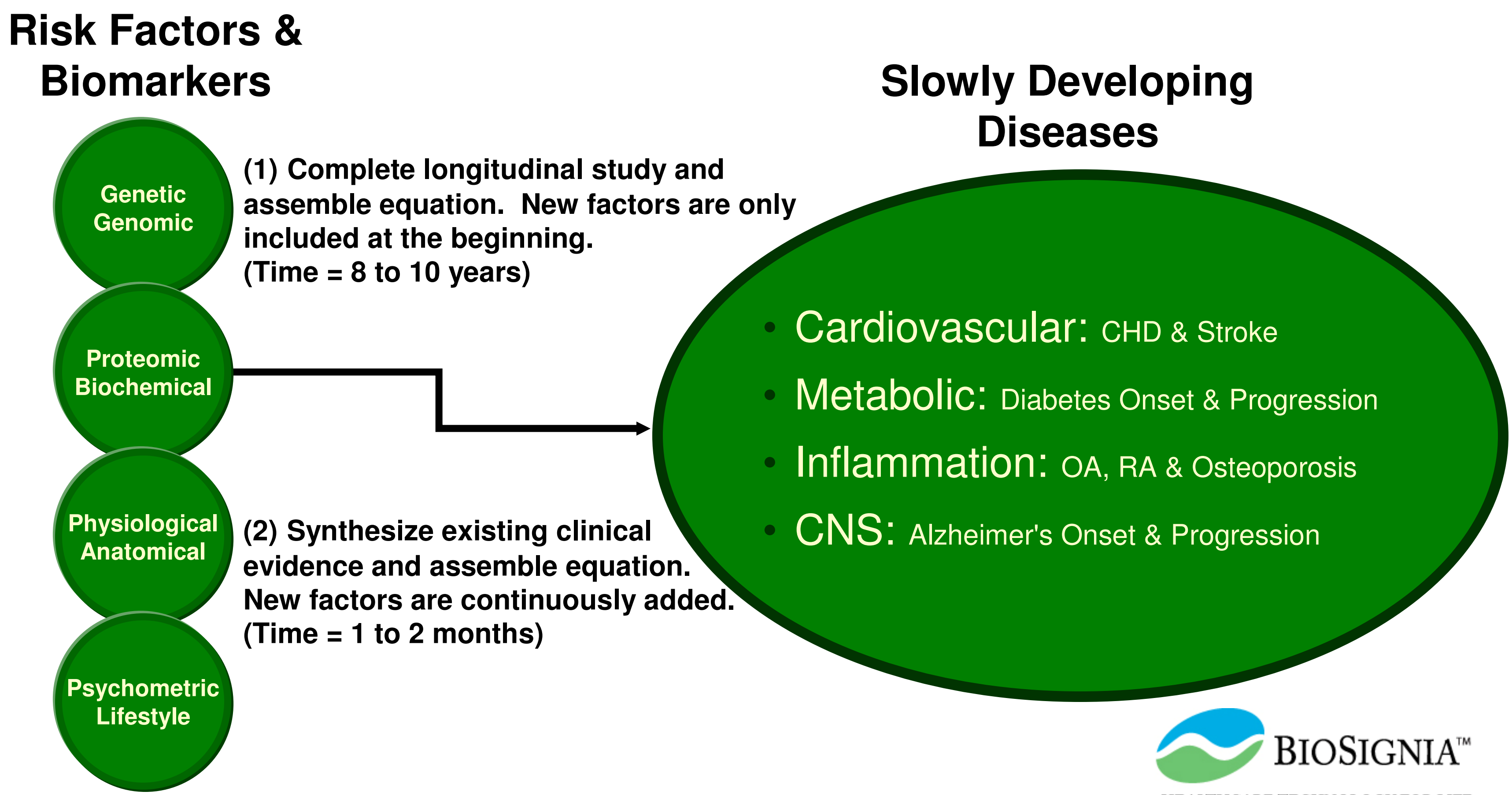
Prediction Methodologies in Risk Assessment

- Non empirical
  - Debit/Credit – health risk assessment and underwriting
- Empirical
  - Based on single study data: multivariate regression analysis
  - Based on multiple study data: multivariate meta-analysis

Key Objective/Goal for Multivariate Prediction Models

- Use <u>all available evidence</u> for any disease state
- <u>Determine probability</u> of onset for specific diseases



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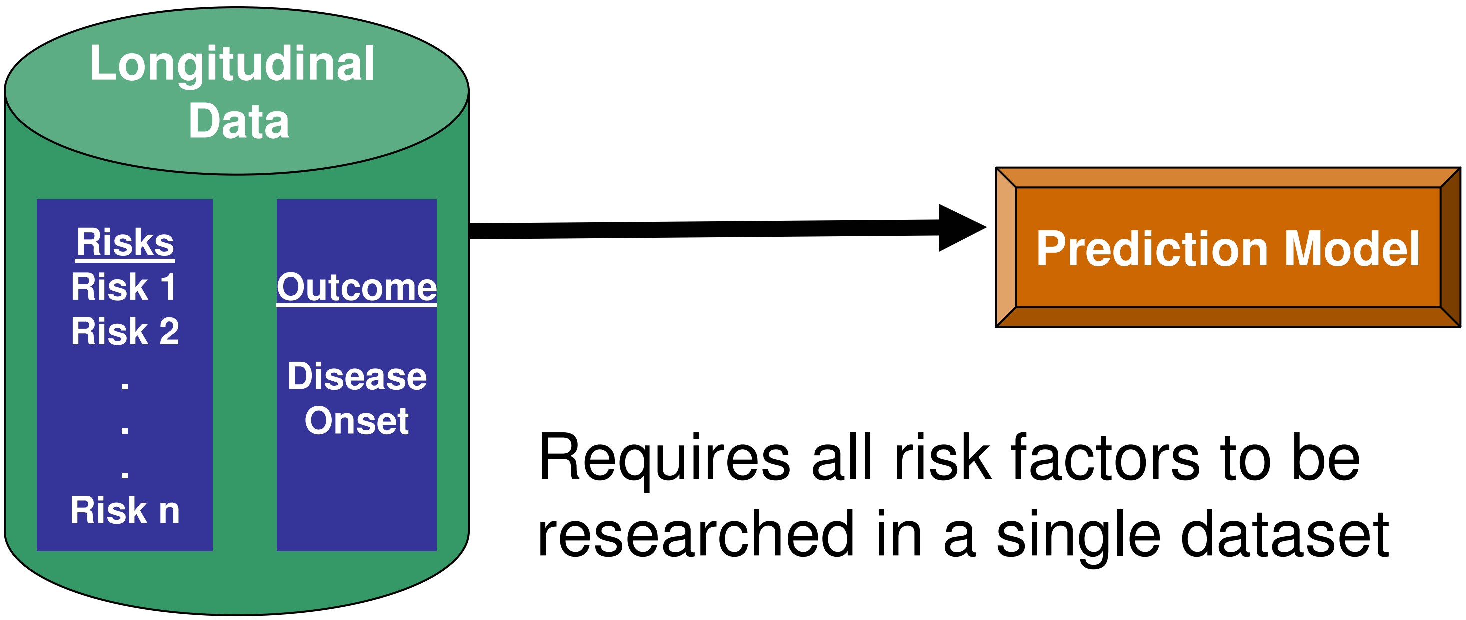
Single Data-Driven Empirical Model

- Study data
  - Longitudinal study
- Statistical Methodology
  - Survival Analysis (proportional hazard model)
  - Life Table
- Examples
  - Framingham CHD model
  - Breast cancer prediction from Nurse Health Study

Single Data-Driven Prediction Model



Requires all risk factors to be researched in a single dataset

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Single Data-Driven Empirical Model

- Advantages
  - Improved accuracy
  - Disease-specific and significant clinical relevancy
  - Used in clinical guidelines, e.g. ATPIII
- Limitations
  - Only one study data, possible selection bias
  - Limited models available
  - Limited risk factors considered
    - Upgrades are slow and always behind
- Methodology
  - Longitudinally-derived multivariate regression technique

Multiple Data-Driven Empirical Model

- Advantages
  - Many disease models can be developed
    - Numerous studies for specific diseases
  - Continuous updating with new discovery
    - Sensitivity and specificity improve more in pace with discovery
    - New markers can be prospectively evaluated
  - Reduced selection bias is possible
  - Overcomes issues associated with co-linearity
- Limitations
  - Longitudinal confirmation
  - Study contributors must be well studied
- Methodology
  - Meta analysis plus Synthesis Modeling™
- Example
  - Know Your Number™ suite of disease prediction models

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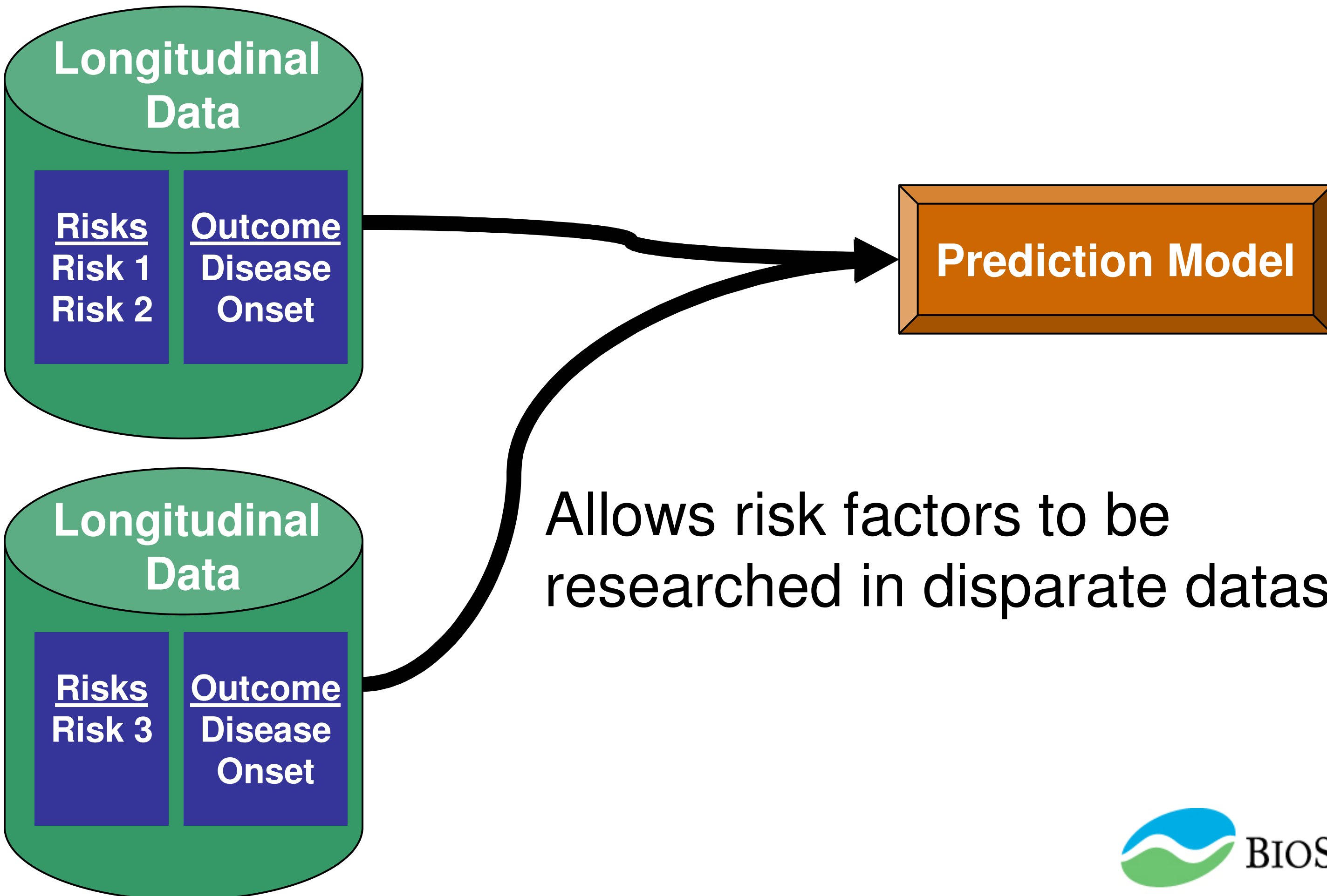
Synthesis Prediction Model



Allows risk factors to be researched in disparate datasets

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Method Overview

STEP 1

- Select disease and predictors.
  - Use only well-tested evidence-based studies
  - Update regularly and monitor continuously
  - Scientific/Technical Policy Committee

STEP 2

- Identify completed outcomes studies with *univariate relative risk* for each factor and disease outcome.
- Combine univariate relative risks by meta-analysis.

STEP 3

- Adjust for co-linearity between factors with cross-sectional study.
- Generate *multivariate* risk equation for all factors.

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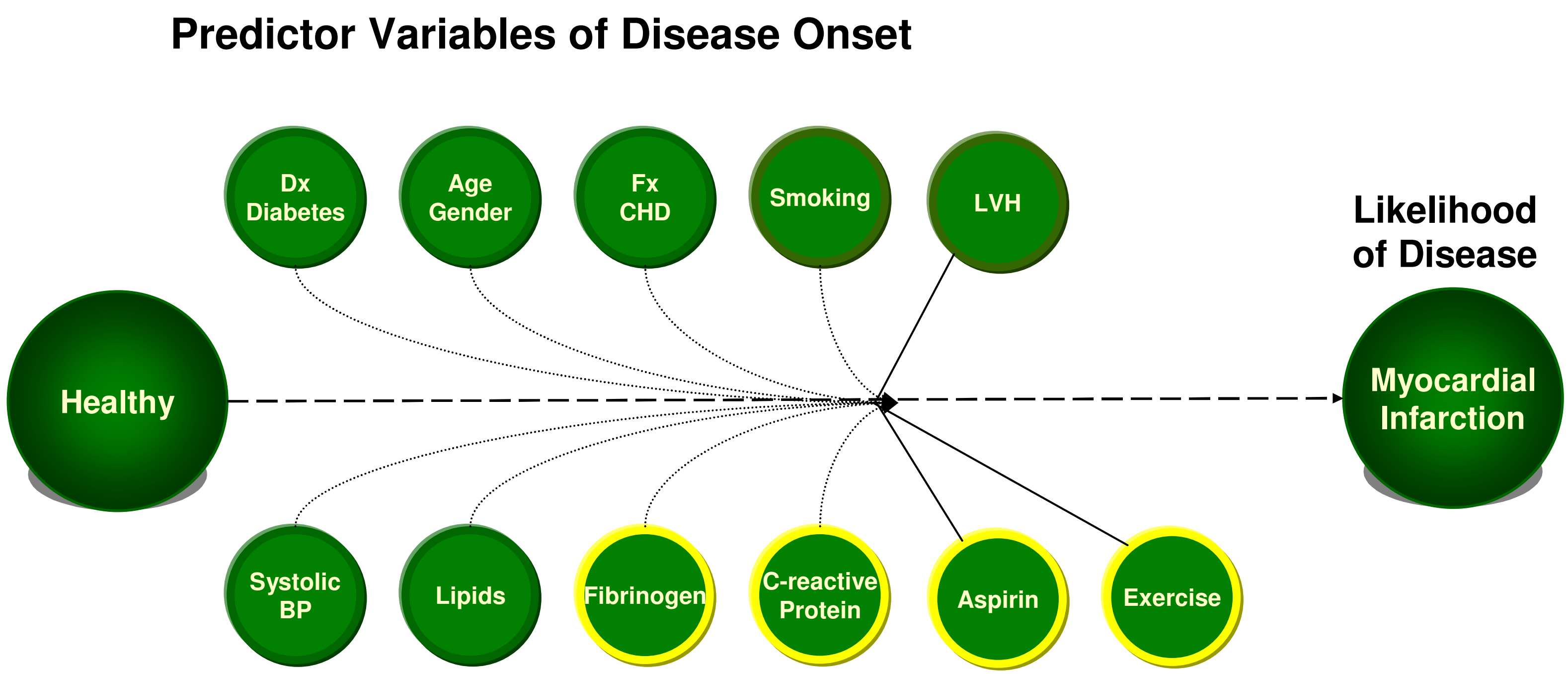
Step 1 – Select Prediction Factors

Coronary Heart Disease



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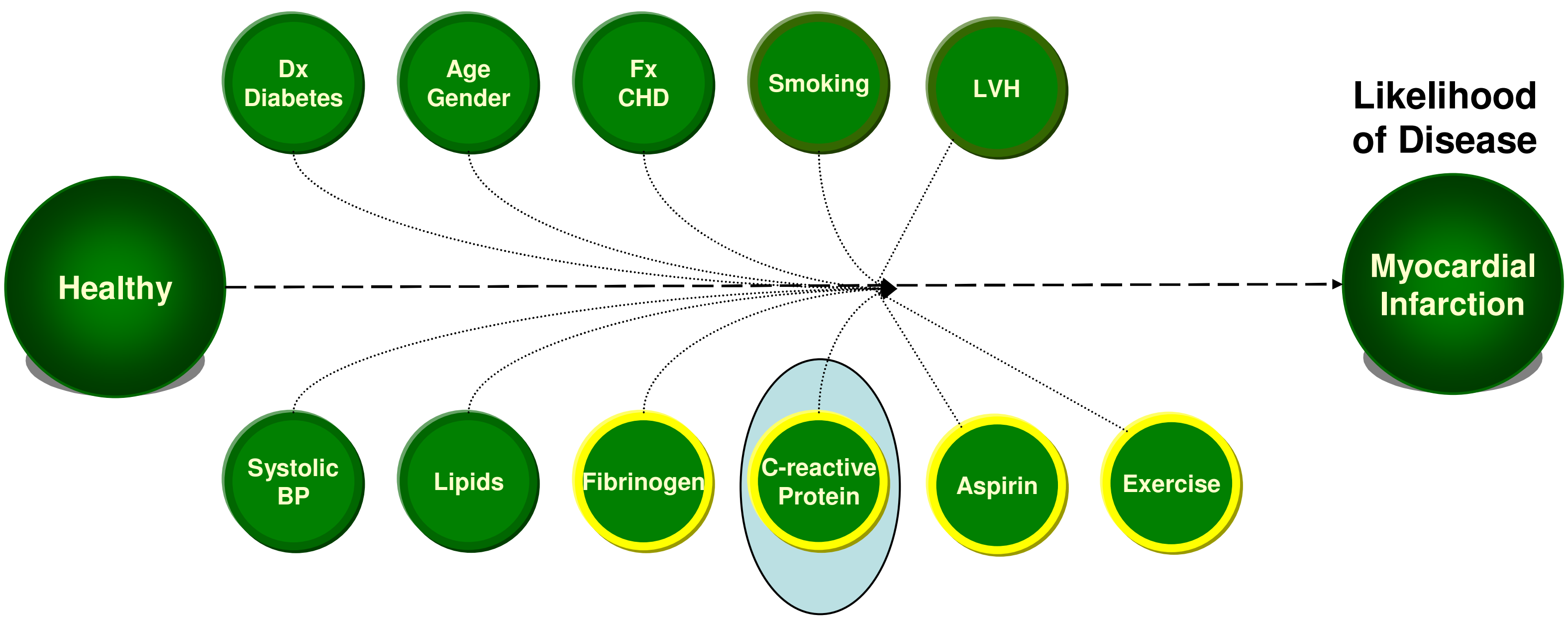
Building an Evidence-based Prediction Model

Coronary Heart Disease

Continuous Update

Predictor Variables of Disease Onset



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The BioSignia Advantage

Continuous ("Evergreen") Improvement

Select CHD Outcome Studies & *Integrate* Predictors

STUDY D
CHD =
LDL-C
SMOKING
SBP

STUDY A
CHD = CRP

STUDY B
CHD = CRP

STUDY C
CHD = CRP

CHD = ß(SBP)+ß(Smoking)+ß(LDL-C)

CHD = ß(CRP)

SYNTHESIS ANALYSIS

- Cross sectional study for colinearity of variables
- Generate partial correlation coefficients
- Integrate variables into one equation

A CHD EVENT = ß(SBP)+ß(Smoking)+ß(LDL-C)+ ß(CRP)

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Validation: Synthesis Analysis™

- Prediction accuracy
  - comparison with other risk assessment methods
- Statistical validation
  - mathematical calculation
  - statistical assumption
- Peer-reviewed publications

Accuracy of Synthesis Modeling™

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Case Study: Accuracy Comparison HRA vs. KYN

- **HRA = Standard Health Risk Assessment using Credit/Debit**
- **KYN = BioSignia's Know Your Number™ using Synthesis Modeling**

- HRA: The Rotterdam Predictive Model (RPM) predicting risk of having undiagnosed type 2 diabetes
  - Risk factors:
    - Age, gender, use of hypertensive medication, BMI
  - Calculation:
    - Debit/credit scoring based on incremental adjustment, e.g. 2 points per 5 year increment over 55, 2 points for Males, 5 points for use of hypertensive drugs, etc.

- KYN: 5 year risk of being diagnosed with type 2 diabetes
  - Risk factors:
    - Age, gender, ethnicity, gestational diabetes, family history, BMI, waist, systolic blood pressure, smoking, exercise, glucose and HDL
  - Calculation:
    - KYN model derived from synthesis analysis
- Evaluation data: NHANES III
  - Outcome: undiagnosed type 2 diabetes according to WHO criteria

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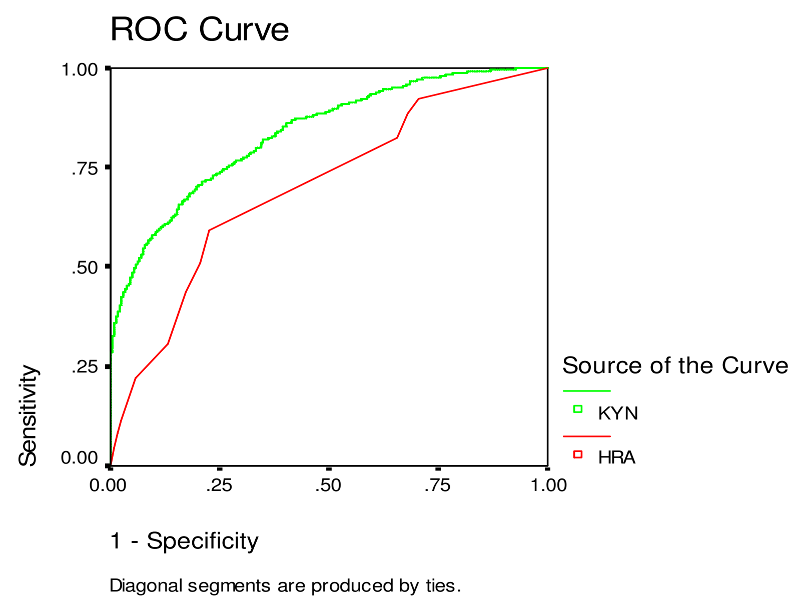
KYN Profiling vs. HRA Profiling

Model	# undiagnosed diabetes cases	# patients predicted to be high risk	Sensitivity
HRA	697	356	51%
KYN	697	482	69%



Conclusion: For identifying undiagnosed cases of type 2 diabetes according to WHO criteria, KYN profiling exceeds performance of Rotterdam HRA by 35%.

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Accuracy Comparison: Synthesized KYN CHD Model vs. Framingham CHD Prediction Model

- Study data:
  - NHANES I with 20 years follow up on CHD death
  - NHANES III, with simulated CHD outcome

1. **Framingham model**
   - Risk factors: age, gender, smoking history, cholesterol, BP, LVH, diabetes
2. **Truncated** KYN Profile CHD model
   - Risk factors: Framingham's plus use of aspirin, exercise, serum albumin
3. **Full** KYN Profile CHD model
   - Risk factors: Truncated model plus family history, lipoprotein (a), homocysteine, C-reactive protein

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KYN CHD Profile vs. Framingham Profile

Data	Model	Sensitivity	Increase
NHANES I (20 years of CHD deaths as outcome)	Framingham	55%	
	Truncated KYN	58%	5%
NHANES III (simulated CHD onset within 5 years)	Framingham	48%	
	Truncated KYN	52%	8%
	Full KYN	55%	14%

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Incremental Increase in Accuracy of KYN over Framingham Model

***Comparable to the contribution of Cholesterol and Blood Pressure to CHD Prediction**

Models	Sensitivity	Increase
Basic (age, gender)	49%	
Basic+cholesterol	51%	5%
Basic+cholesterol+BP	53%	8%

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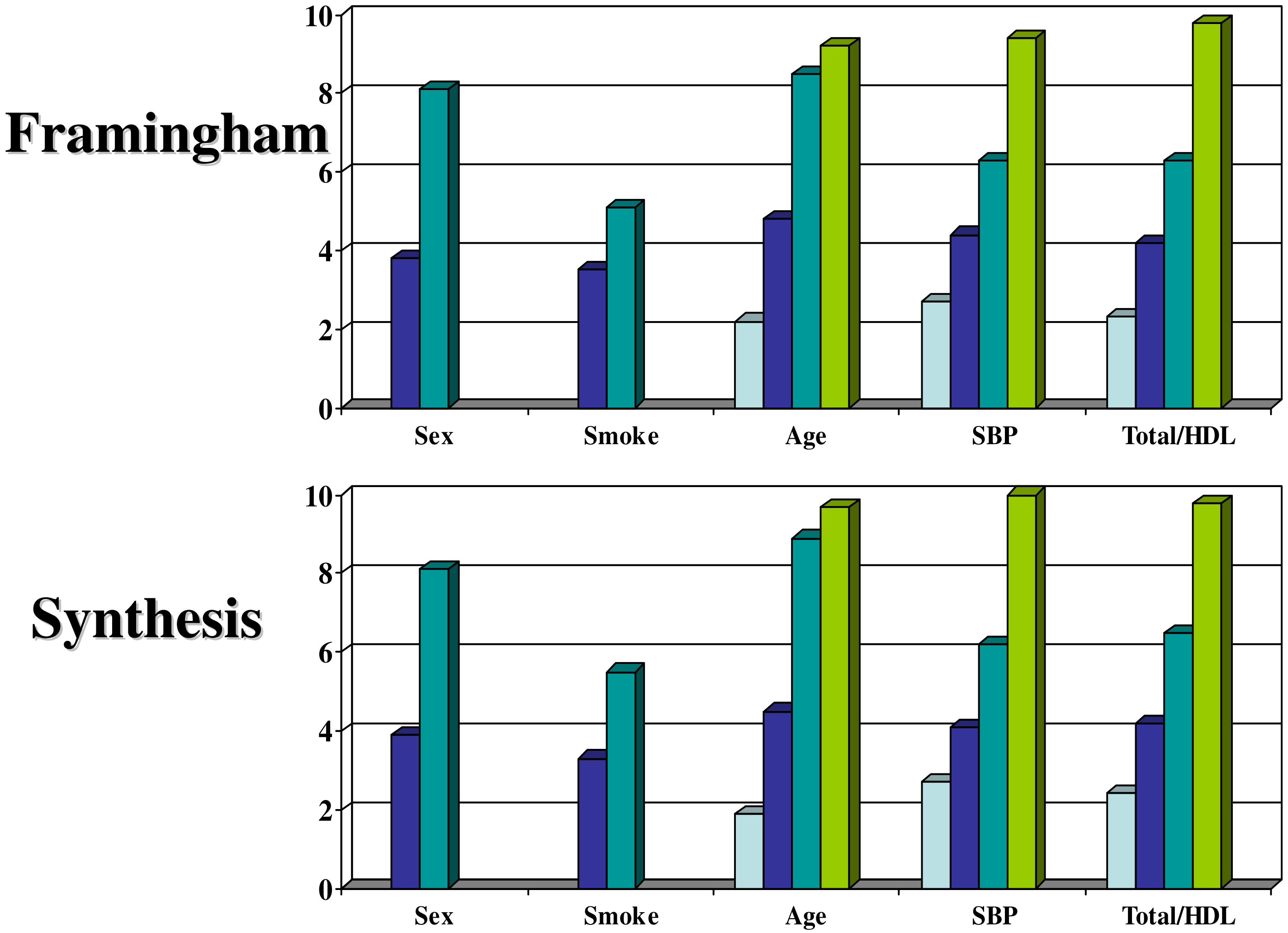
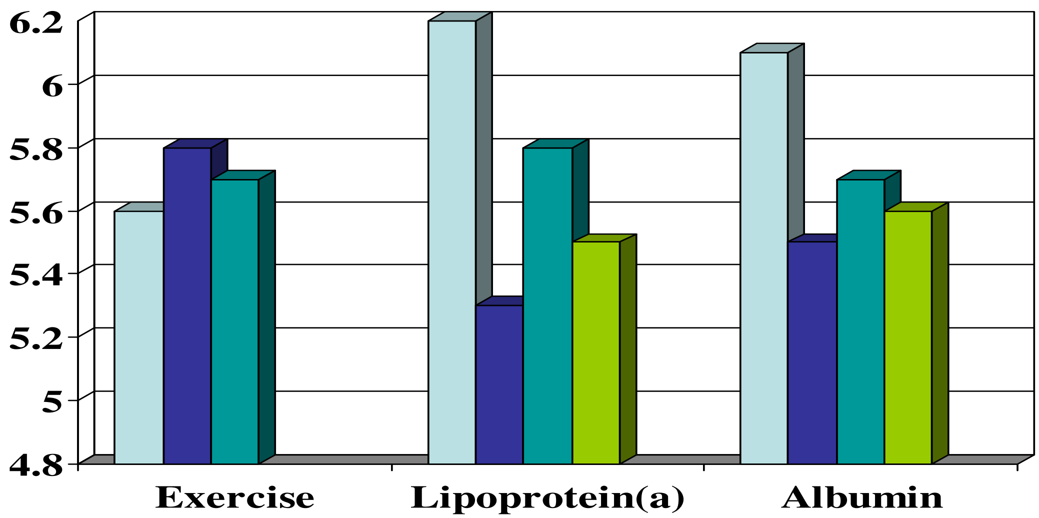
Prediction among NHANES III population using risk factors considered by both models

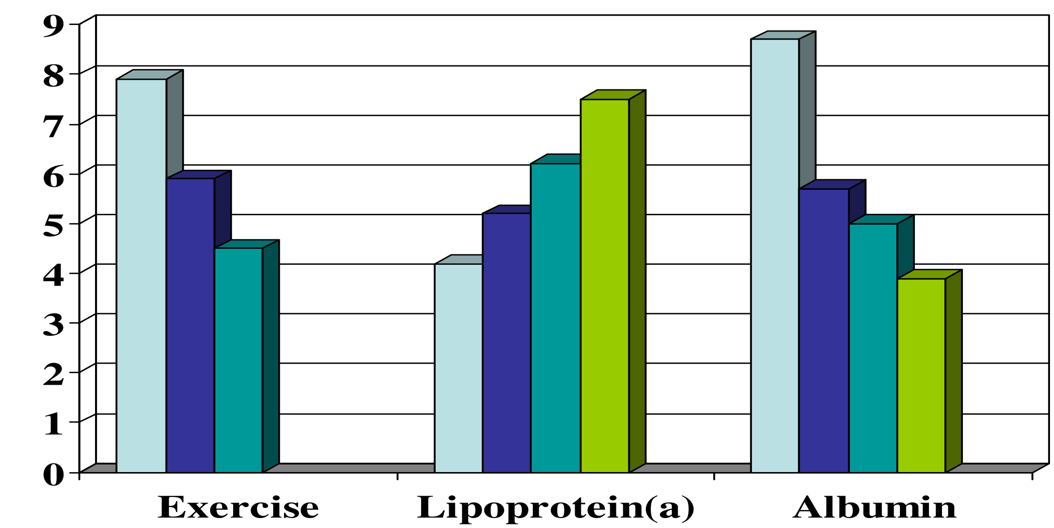


Prediction among NHANES III population using risk factors considered by synthesized model only

Framingham



Synthesis



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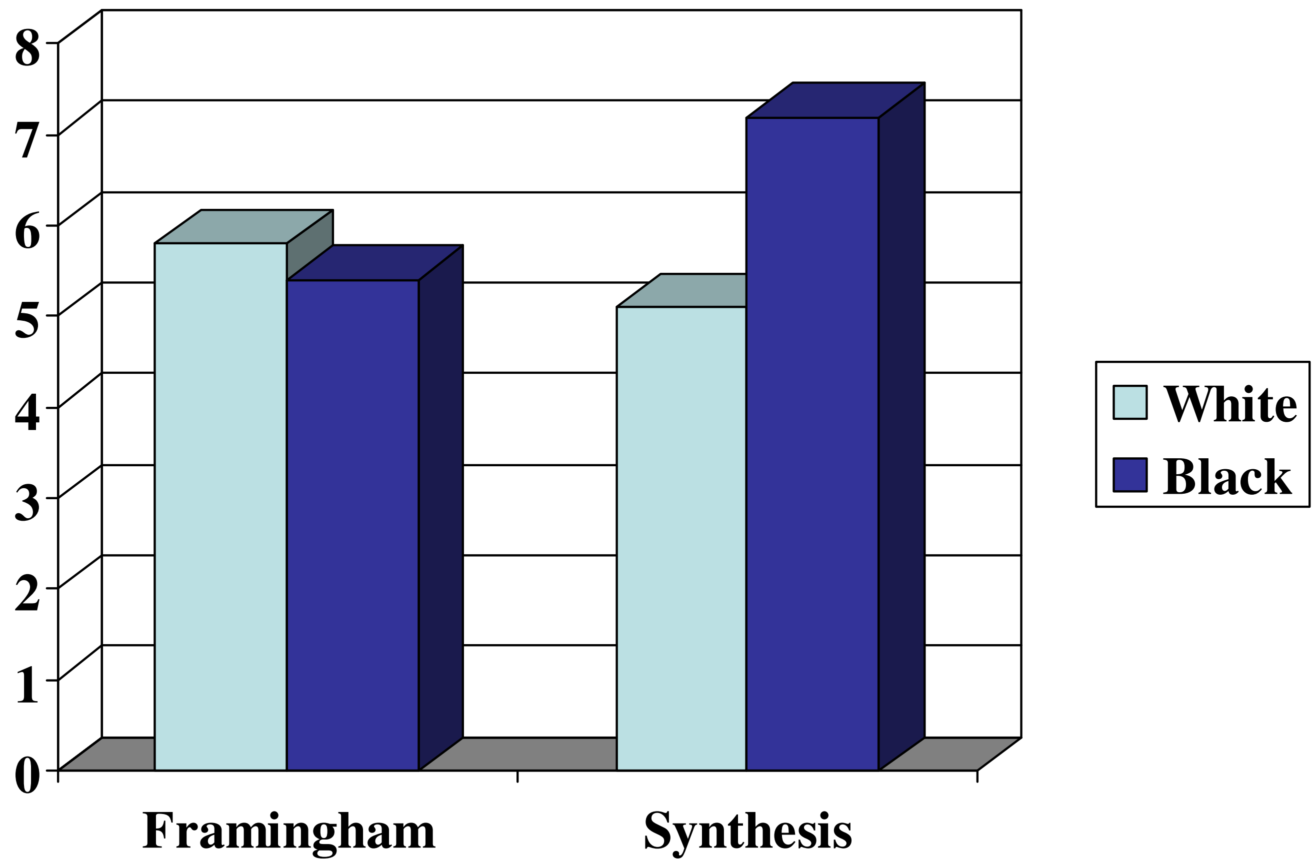
Prediction among NHANES III populations using risk factor considered by neither model



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Statistical Validity of Synthesis Analysis™

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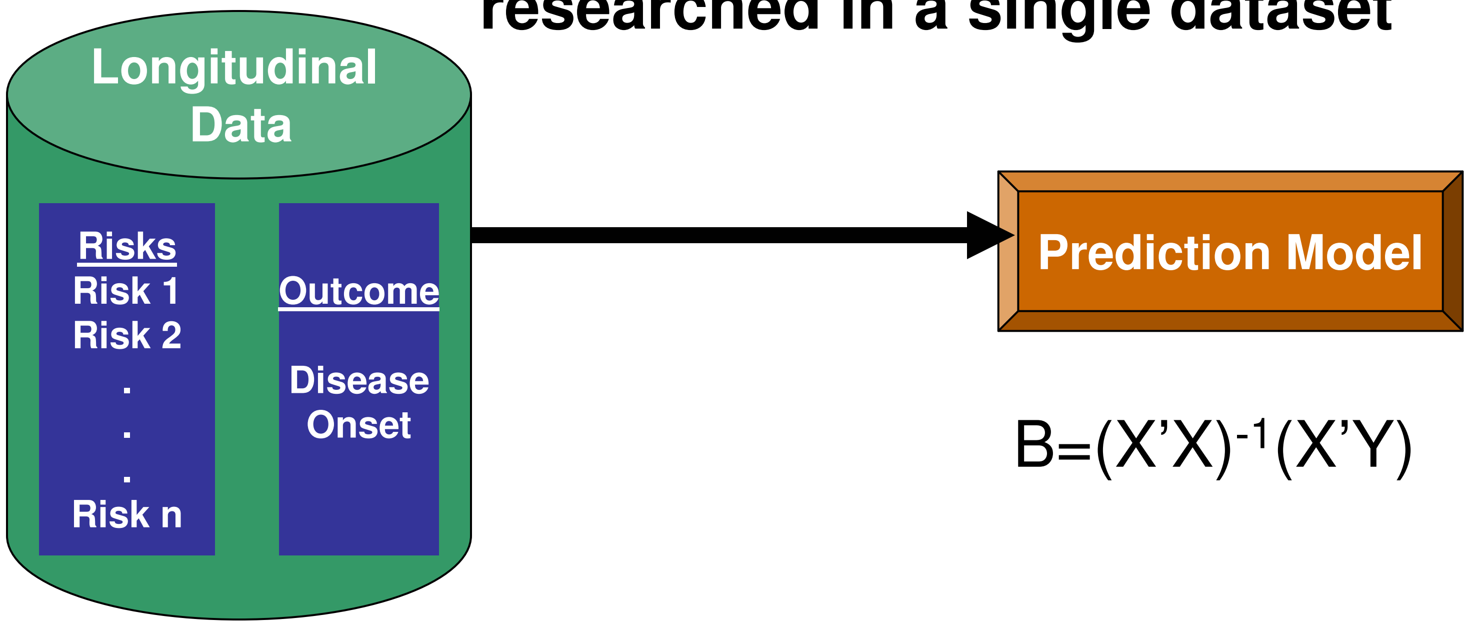
Conventional Prediction Model

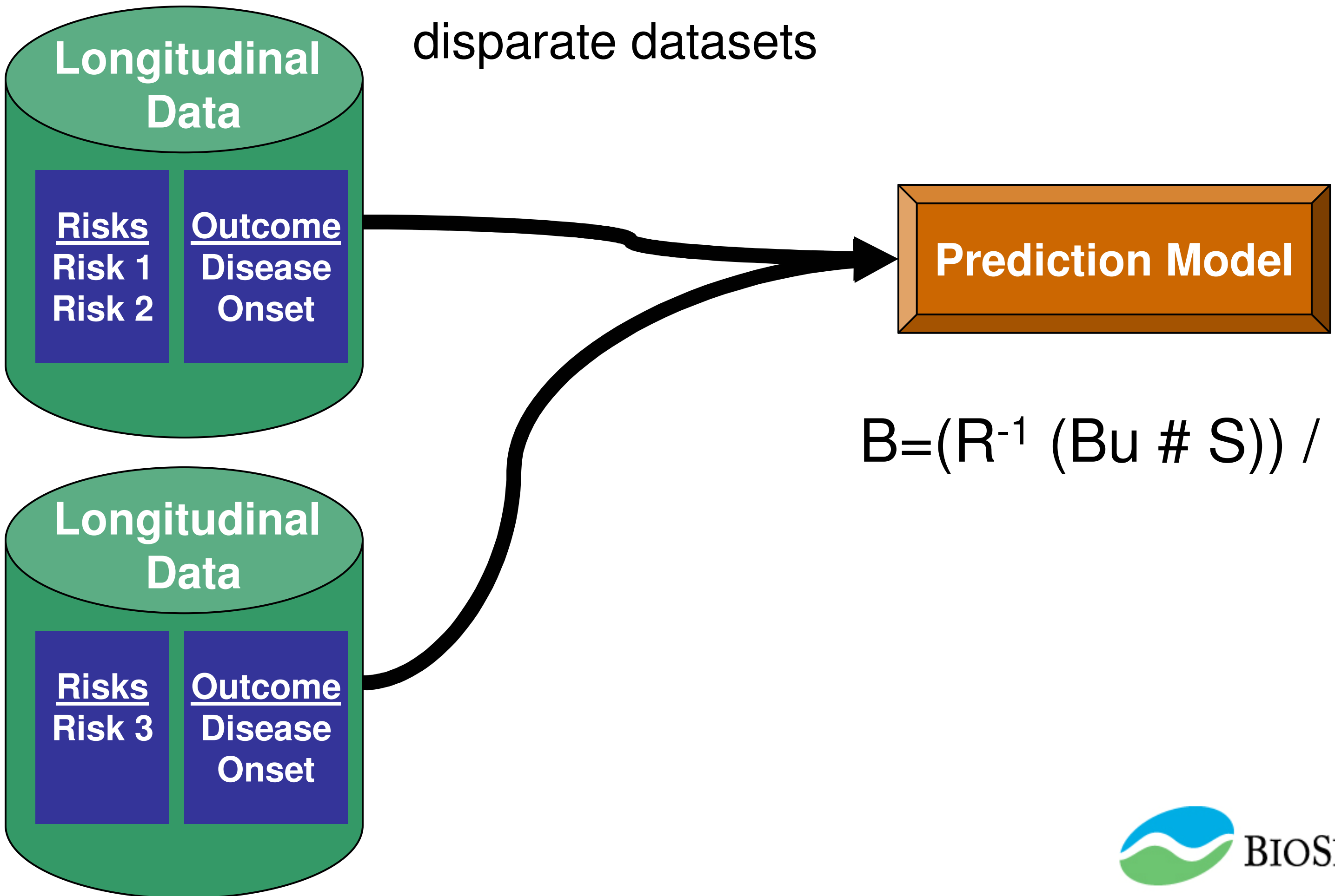
Requires all risk facts are researched in a single dataset



$$B=(X'X)^{-1}(X'Y)$$

Synthesis Prediction Model

Allows risk factors to be researched in disparate datasets



$$B=(R^{-1}\ (Bu\ \#\ S))\ /\ S$$

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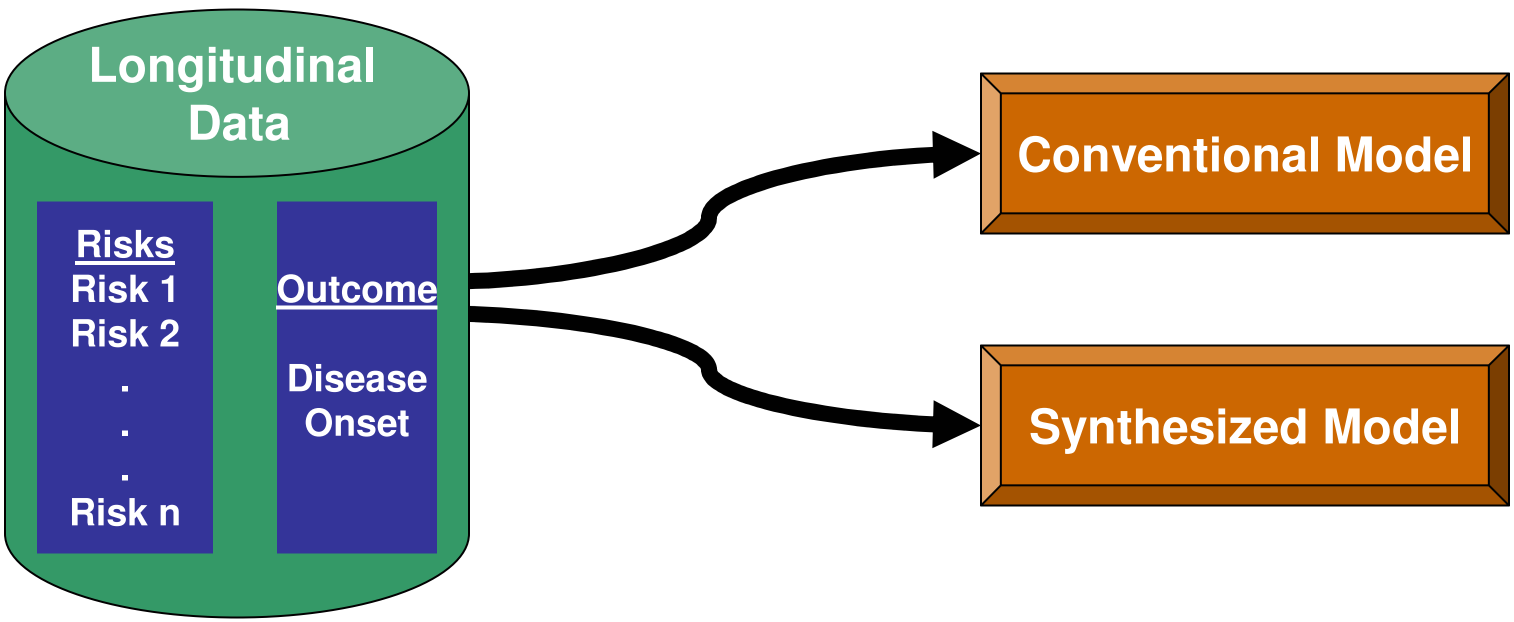
Test the Mathematical Calculation

Is synthesized model equal to conventional model when the data input is the same?



Mathematically equivalent

$$(X'X)^{-1}(X'Y) = (R^{-1}\ (Bu\ \#\ S))\ /\ S$$

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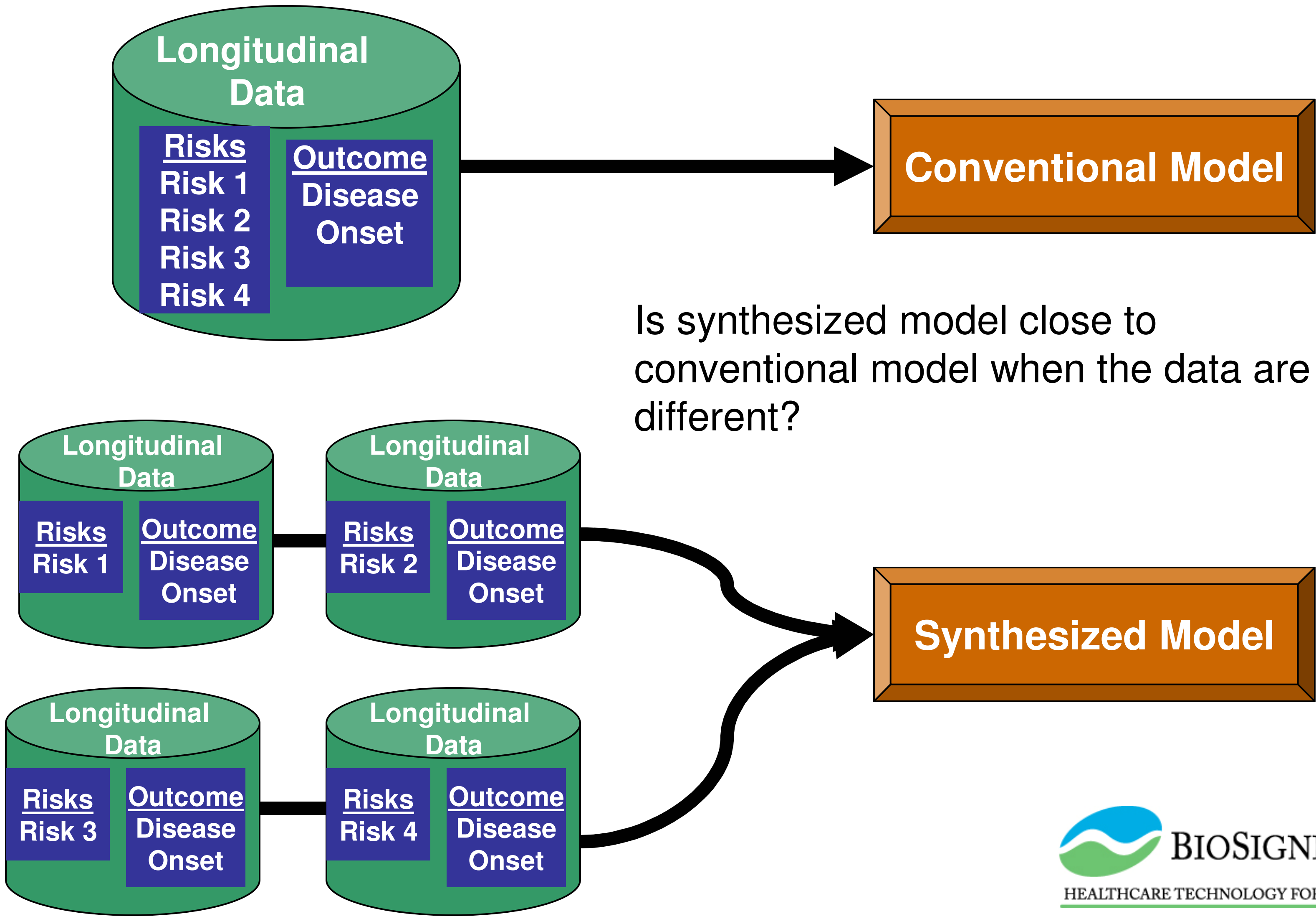
Test the Statistical Assumptions



Is synthesized model close to conventional model when the data are different?

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Validate the Assumptions Through Simulation

1. Treat the conventional regression as a gold standard.
2. Add perturbation to each input variable representing the variation derived from different data sources.
3. Compute the prediction based on the synthesized equation using data with perturbation.
4. Run correlation between prediction from gold standard and synthesized prediction.
5. Collaboration and publication with Duke Center for Clinical and Health Policy Research.

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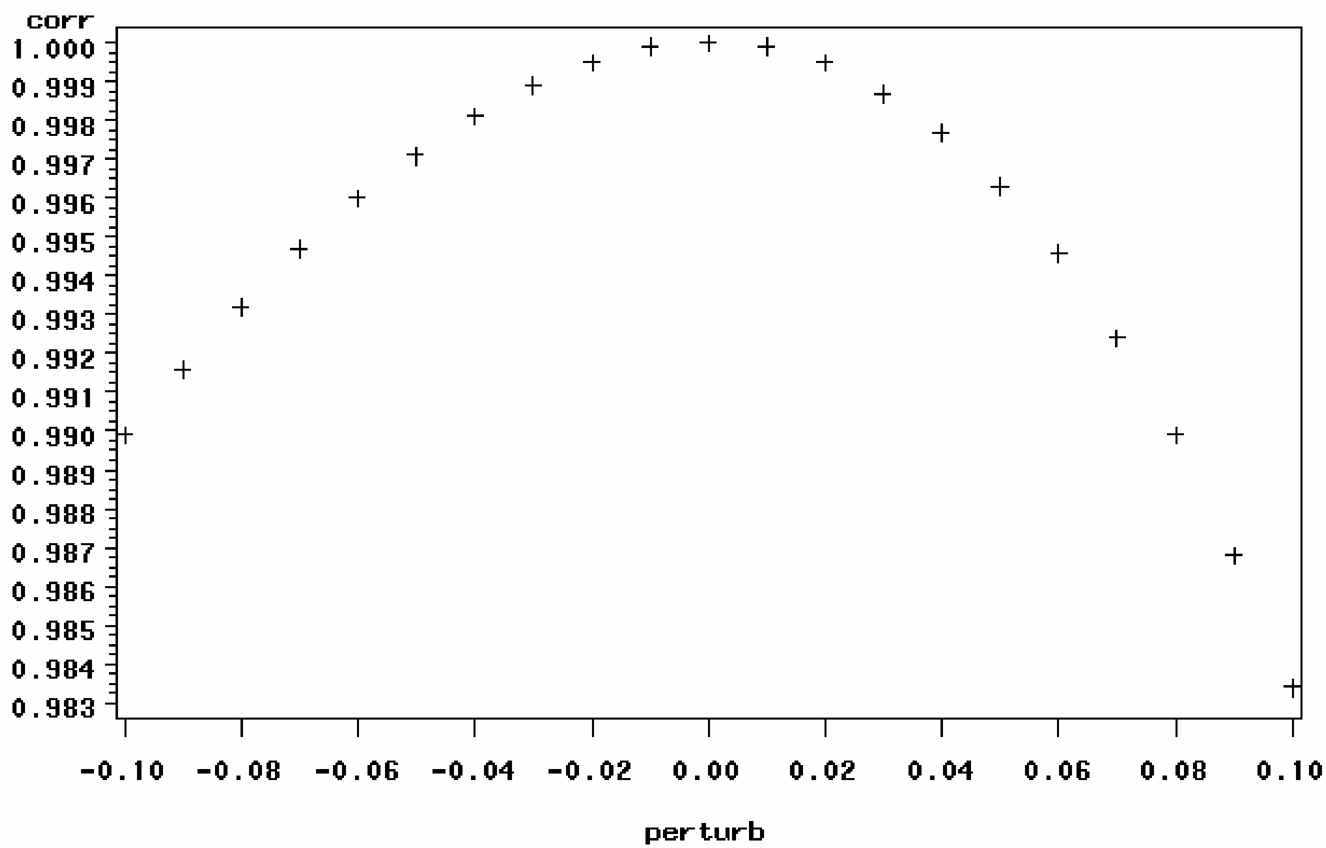
Simulation Results



Effect of perturbing R on correlation

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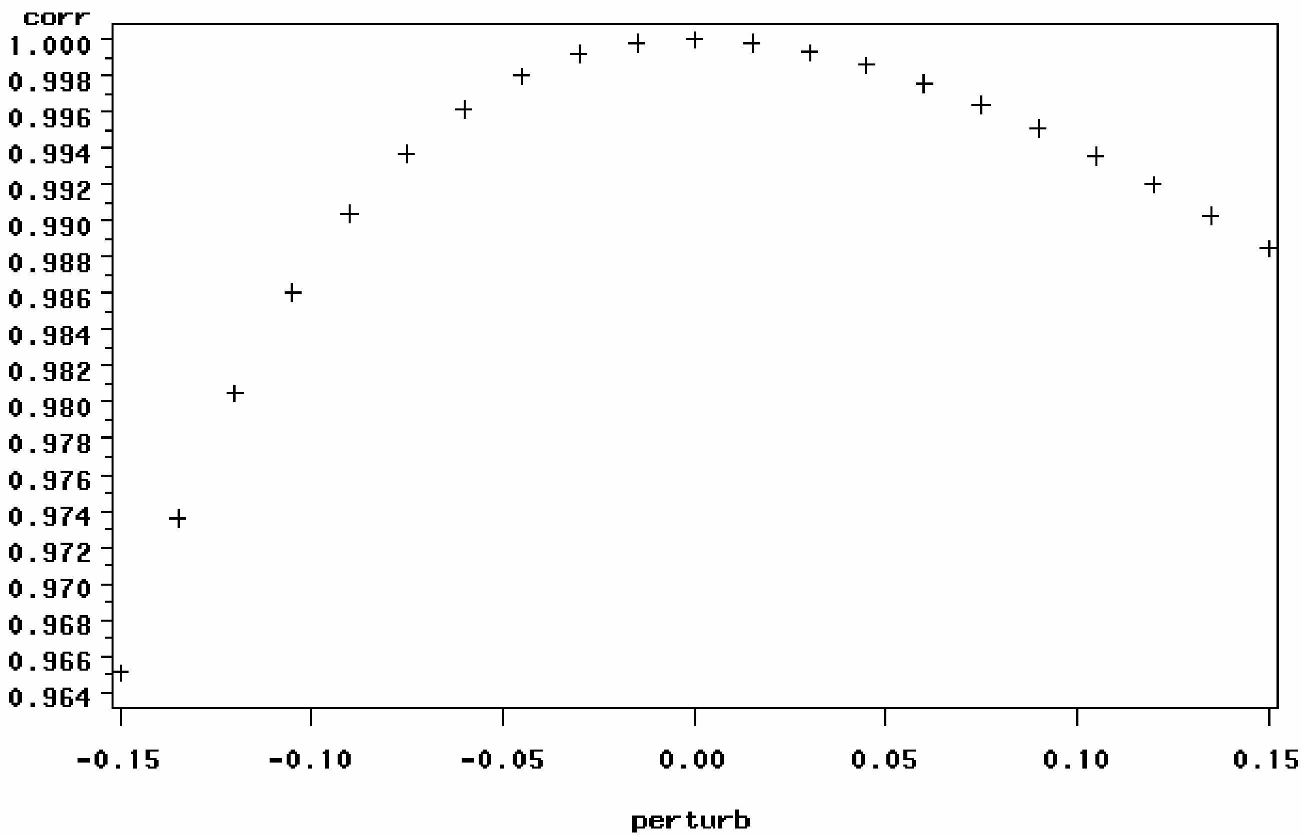
Simulation Results



Effect of perturbing B_u on correlation

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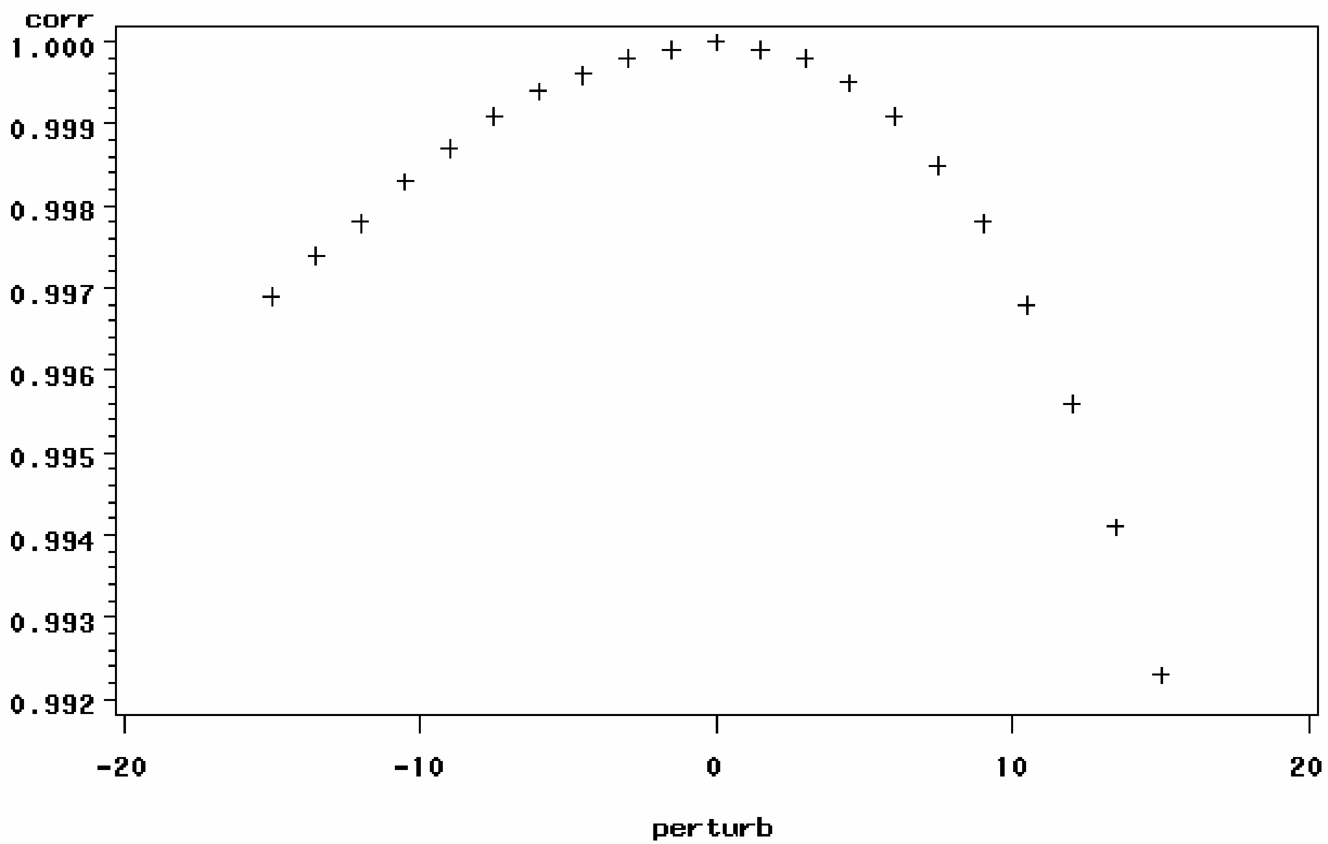
Simulation Results



Effect of perturbing S on correlation

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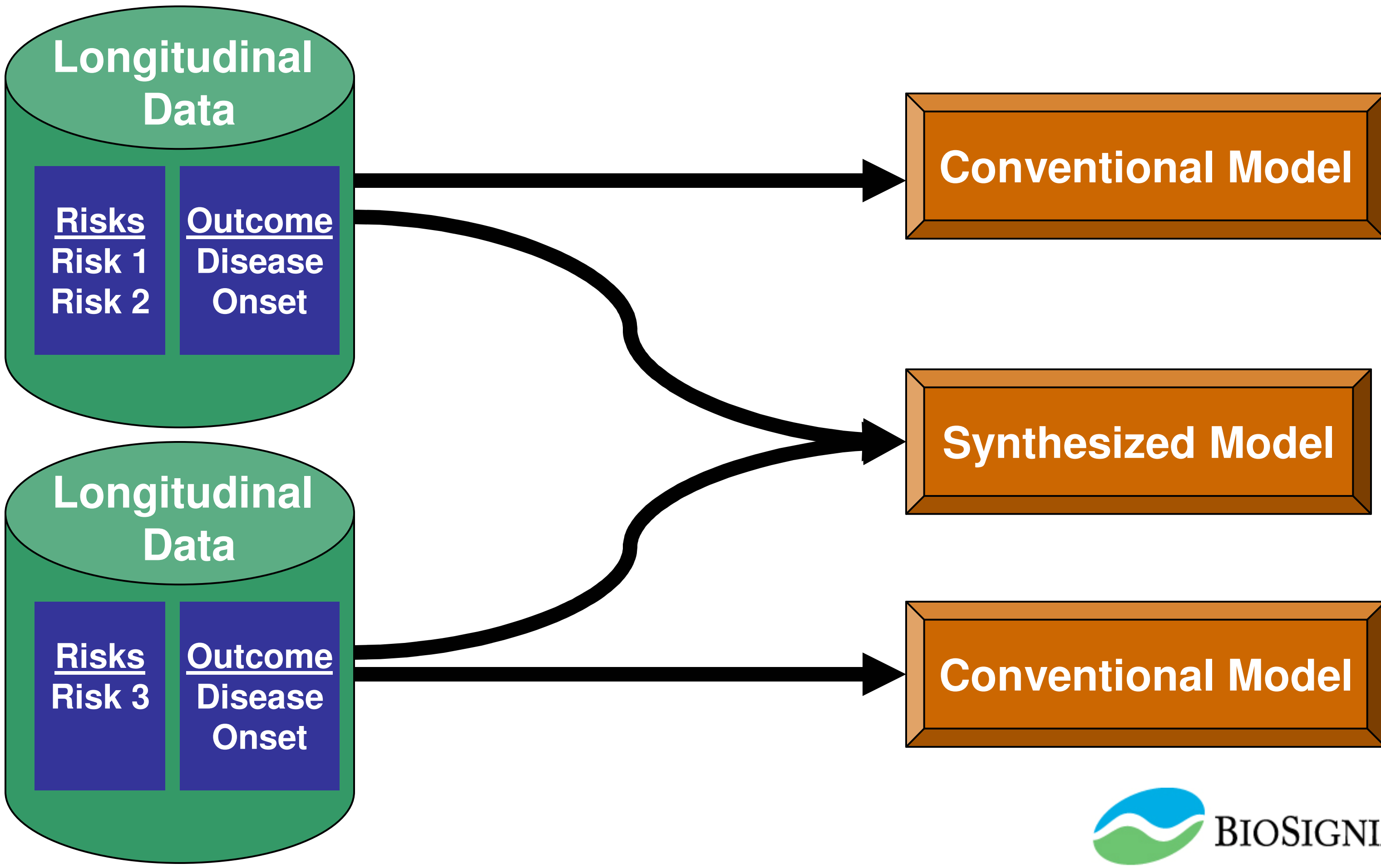
The Benefit of Synthesis Analysis™

Synthesized Model Better Than Conventional Model



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Advantage of Synthesized Model
(adding new risk factors)

Risk factors included in logistic model	Additional risk factor added by synthesis model	Area under ROC	
		Logistic	Synthesis
Sex, age	cholesterol	0.641	0.662
Sex, age, cholesterol	SBP	0.663	0.673
Sex, age cholesterol, SBP	BMI	0.674	0.679
Sex, age, SBP, cholesterol, BMI		0.680	

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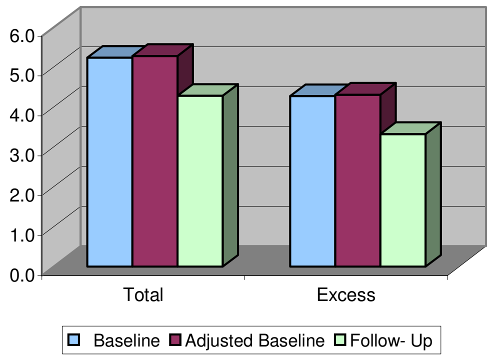
Benefits of Synthesis Analysis™

- Improved prediction accuracy
- Allows more comprehensive models
- More representative of the population
- Easy to update
- Significant clinical relevance

Case Study I: KYN + Health Intervention

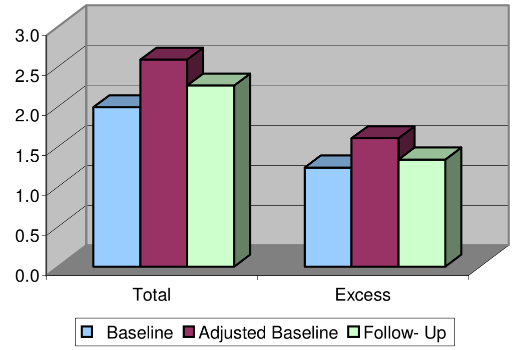
Type 2 Diabetes

Predicted Cases	Baseline	Adjusted Baseline	Follow-Up	Change %	P Value
Total	5.2	5.3	4.3	-19%	0.00
Excess	4.3	4.3	3.3	-23%	0.00



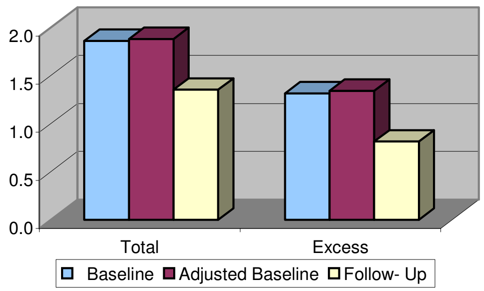
Coronary Heart Disease

Predicted Cases	Baseline	Adjusted Baseline	Follow-Up	Change %	P Value
Total	2.0	2.6	2.3	-16%	0.03
Excess	1.2	1.6	1.3	-21%	0.05



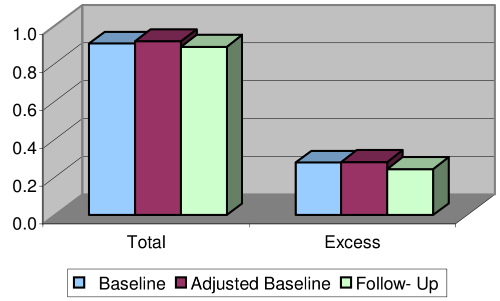
Stroke

Predicted Cases	Baseline	Adjusted Baseline	Follow-Up	Change %	P Value
Total	1.9	1.9	1.4	-28%	0.00
Excess	1.3	1.3	0.8	-39%	0.00



Heart Failure

Predicted Cases	Baseline	Adjusted Baseline	Follow-Up	Change %	P Value
Total	0.9	0.9	0.9	-3%	0.58
Excess	0.3	0.3	0.2	-13%	0.08



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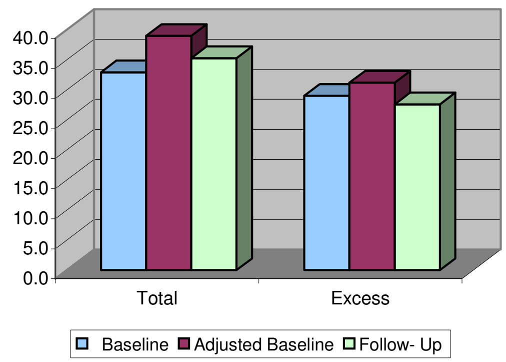
Case Study II: KYN
Without Additional Intervention

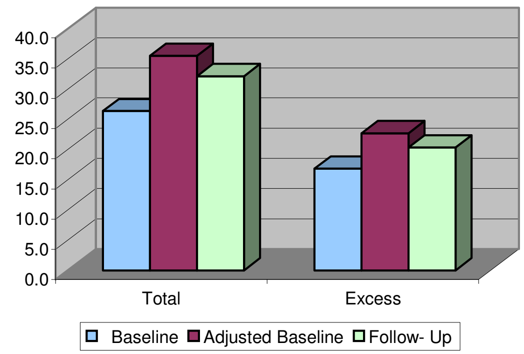
Type 2 Diabetes

Predicted Cases	Baseline	Adjusted Baseline	Follow-Up	Change %	P Value
Total	32.9	39.0	35.3	-10%	0.02
Excess	29.0	31.2	27.6	-12%	0.01

Coronary Heart Disease

Predicted Cases	Baseline	Adjusted Baseline	Follow-Up	Change %	P Value
Total	26.4	35.5	32.2	-13%	0.00
Excess	16.8	22.7	20.4	-14%	0.00



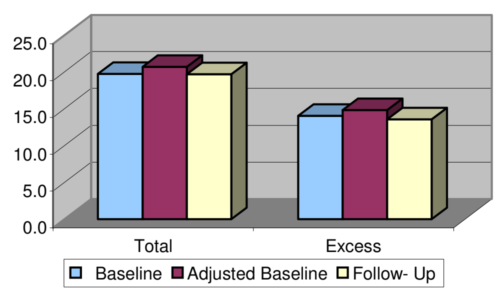


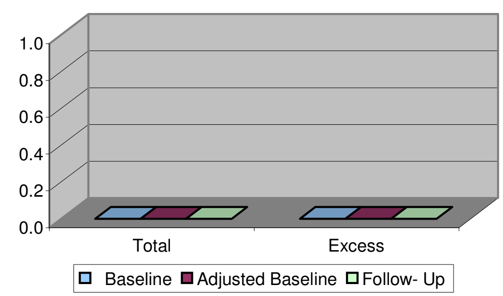
Stroke

Predicted Cases	Baseline	Adjusted Baseline	Follow-Up	Change %	P Value
Total	19.7	20.7	19.7	-5%	0.03
Excess	14.0	14.8	13.6	-8%	0.01

Heart Failure

Predicted Cases	Baseline	Adjusted Baseline	Follow-Up	Change %	P Value
Total	N/A	N/A	N/A	N/A	N/A
Excess	N/A	N/A	N/A	N/A	N/A





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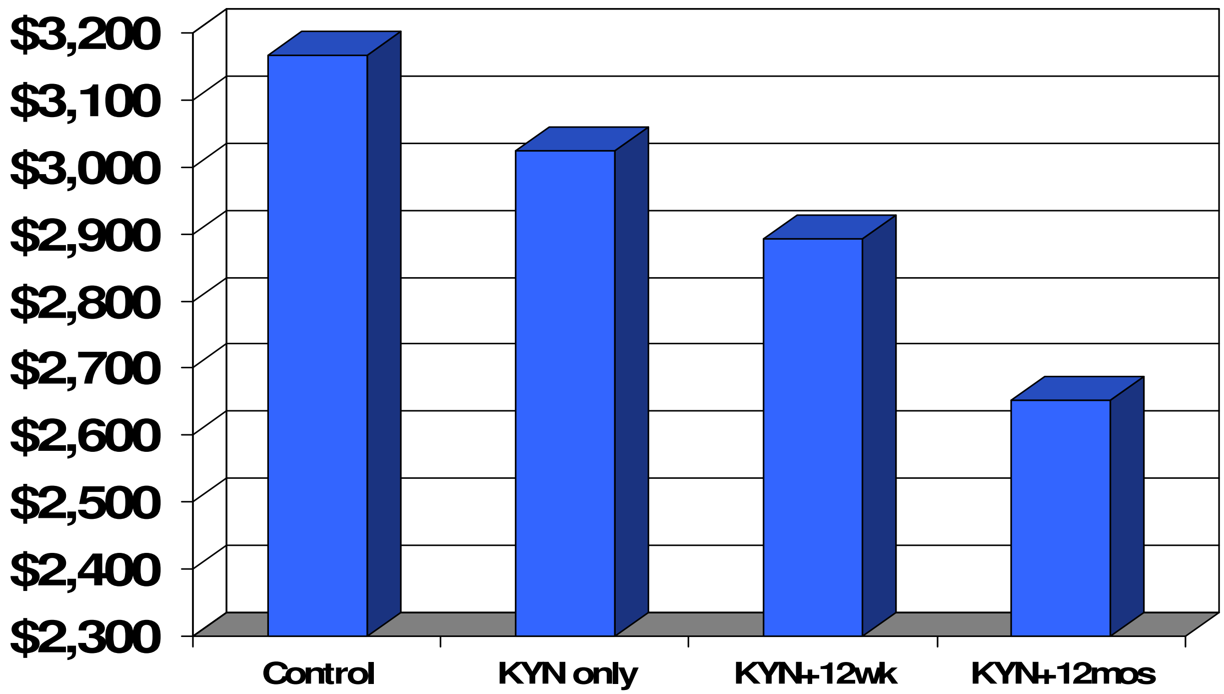
KYN Decreases Medical Costs

Average cost
per year



Data from State of North Carolina Employees Program

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Selected Publications

Hu, G. and Root, M. Building prediction models for coronary heart disease by synthesizing multiple longitudinal research findings. European Journal of Cardiovascular Prevention and Rehabilitation, **12**:459-464 (2005).

Root, M. and Smith, T. Prescribe by risk: The utility of a biomarker-based risk calculation in disease management to prevent heart disease. Disease Management, **8**:106-113 (2005).

Samsa, G., Hu, G., and Root, M. Combining information from multiple data sources to create multi-variable risk models: illustration and preliminary assessment of a new method. Journal of Biomedicine & Biotechnology, **2**:113-123 (2005).

Cobb FR, Kraus WE, Root M, Allen JD. Assessing risk for coronary heart disease: Beyond Framingham. American Heart Journal **146**:572-580 (2003)

Root, M. Risk stratification creates more cost-effective health promotion. Oral presentation at the 4th Annual North Carolina Alliance for Healthy Communities Conference, Chapel Hill, NC, October 21, 2004

Root, M. Biomarker panels versus single biomarkers to predict clinical endpoints. Invited oral presentation at the 10th EUFEPS Conference on Optimizing Drug Development: Getting the Dose Right, December 9-11, 2002.

Root M, Hu G, and Chimera J. Selecting therapeutic targets for preventing heart disease using a novel predictive model. Poster presentation at EB02. See FASEB Journal 16: Abstract #691.20 (2002)

Hu, G and Root, M. Developing disease-specific and morbidity-based health risk assessment. Oral presentation at the 36th Annual Meeting of the Society of Prospective Medicine, Sept. 23-26, 2000.

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END

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